REMARKS/ARGUMENTS

Applicants would like to take this opportunity to thank Examiner Lankford for granting a personal interview with Applicants' agent on July 8, 2003. By this amendment, claim 3 is canceled; claims 1, 2, 11, 13, 18-21, 27, and 32-36 are amended; and new claim 37 has been added. No new matter has been introduced. Claims 1, 2, 4-37 are pending. Allowance of all pending claims are respectfully requested.

Rejections under 35 U.S.C. §103

Claims 1-36 stand rejected under 35 U.S.C. §103(a) as obvious over Adlam et al. and Evans et al. and Fujiwara et al., and Howard et al. and Megid et al. and Neifeld et al. Applicants respectfully traverse the rejection.

The instant invention claims methods for inducing the regression of dermal tumors and warts caused by the human papilloma virus or for treating infections of the upper-and-lower respiratory tract in humans by administering a bacterial product comprising heat-killed, terminally sterilized *P. acnes, P. avidum, P. lymphophilum, P. granulosum, C. parvum* and *A. propionica.* The claims are supported by the examples showing: (1) effective treatment of human patients with plantar warts with intralesional and subcutaneous administration of heat-killed, terminally sterilized *P. acnes* (Example 3); (2) effective treatment of human patients with clinical signs of upper and lower respiratory infections, which are manifested as sore throat, ear ache, and cough (Example 1); and (3) clinical toxicity study of *P. acnes* in human subjects, which demonstrated the safety of the *P. acnes* treatment.

Adlam reports that intravenous injection of formalin-inactivated *P. acnes* stimulates the lympho-reticular system in mice.

Howard reports that inactivated *P. acnes* augments the B cell response to the thymus-independent antigen SIII in mice.

Evans provides that intravenous injection of inactivated *P. acnes* can be used as an adjunct to conventional therapy to increase the rate of recovery from equine respiratory diseases.

Fujiwara describes that injection of *P. acnes* reduces tumor metastasis, but not primary tumor growth in mice.

Megid et al. authorized three references [Megid et al. Vaccine 17 (1999), 2446 (Megid I); Megid et al. Rev. Inst. Med. trop. S. Paulo 41 (1999), 107 (Megid II); and Megid et al.

Comparative Immunology, Microbiology & Infectious Diseases 23 (2000), 91 (Megid III)]. Magid I demonstrates that administration of *P. acnes* as an adjuvant for an anti-rabies vaccine may affect humoral and cellular response, but does not reveal any encouraging results. Megid II and III, on the other hand, show that *P. acnes* treatment improves the survival rate of mice infected with rabies virus.

Neifeld describes that preoperative intratumoral injection of *P. acnes* and postoperative subcutaneous injection of *P. acnes* are ineffective when used as an adjuvant to surgery for primary cancers of the oral cavity, pharynx, and larynx.

Applicants respectfully submit that the cited references do not teach nor suggest using *P. acnes* as a treatment for dermal tumors and warts caused by the human papilloma virus or upper-and-lower respiratory tract infections in humans. With regard to dermal tumors and warts, none of the cited references teaches or suggests treating skin diseases with *P. acnes*. With regard to respiratory tract infections, only Evans provides that *P. acnes* can be used as an adjunct to conventional therapy to increase the rate of recovery from equine respiratory diseases. Evans, however, does not teach or suggest using *P. acnes* alone as a treatment for equine respiratory diseases.

The Office Action asserts that "[t]here is a reasonable expectation that stimulating the immune system will aid a body in its defense against a tumor or infection." Applicants respectfully disagree. It was well known in the art at the time of the invention that an immune stimulant may not necessarily have anti-neoplastic and/or antiviral effect, and that an immune stimulant that is effective in treating one disease may not be effective in treating another disease. The effect of the non-specific immune stimulants seems to depend on many factors, such as the host immune state, severity of infection, dose and timing of drug administration, *etc.*

In the case of *P. acnes*, there are variable published results and paradoxical findings from different laboratories at the time of the invention about its effectiveness in treating tumors and bacterial infections. For example, Megid II shows that administration of *P. acnes* improves the survival rate of mice infected with rabies virus, but Megid I shows the treatment is not effective as an adjuvant for an anti-rabies vaccine in mice. Similarly, while Fujiwara describes that injection of *P. acnes* reduces the metastasis of plasmacytoma, Neifeld demonstrates that treatment with *P. acnes* is ineffective for primary cancers of the oral cavity, pharynx, and larynx.

Out of the eight cited references, Adlam and Howard do not show any therapeutic results. Megid I and Neifeld demonstrate that *P. acnes* treatment is not effective for rabies virus and a number of primary cancers. Fujiwara provides that the *P. acnes* treatment reduces tumor metastasis, but not primary tumor growth. Only Magid II, Magid III and Evans report some positive result in using *P. acnes* for treating rabies virus (Magid II and III) and as an adjunct to conventional therapy for equine respiratory diseases (Evans).

Taken together, Applicants respectfully submit these references do not support the Office Action's conclusion that " [t]he huge breadth of teachings in the art give the skilled artisan a reasonable expectation of success to treat neoplastic or viral maladies." This conclusion is further supported by the fact that, at the time of the present invention, *P. acnes* was found ineffective in the treatment of primary breast cancer (Brown et al., Cancer, 15:220, 1990); experimentally induced coloform mastitis (Jhogan et al., J Dairy Sci 77:462, 1994), and chronic Staphylococcus aureus mastitis (Dinsmore et al., ., J Dairy Sci 78:1932, 1995).

The Office Action also asserts that " [a]pplicant's claims are not drawn to specific diseases but classes thereof, nor do the claims require a specific level of treatment." Applicants have amended the claims to focus on the treatment of "dermal tumors and warts caused by the human papilloma virus." In the field of dermatology, warts is defined as a skin disease caused by infection of human papilloma virus (See, for example, American Academy of Dermatology's web site at http://www.aad.org/pamphlets/warts.html). Since applicants have demonstrated effective treatment of warts with *P. acnes*, it is reasonable to conclude that P. acnes treatment would be effective against skin diseases caused by the human papilloma virus, *i.e.*, dermal tumors and wards. Similarly, applicants do not claim treatment for any respiratory diseases, but only "viral infections of upper and lower respiratory tract with clinical manifestation of sore throat, ear ache or cough," which, again, is supported by the experimental evidence (Example 1). Accordingly, applicants' claims are drawn to specific diseases.

Furthermore, none of the cited references teaches or suggests the use of terminally sterilized *P. acnes* for the treatment of neoplastic or viral diseases. Among the eight references, only Adlam and Fujiwara disclose the inactivation procedure for *P. acnes* (formalin in Adlam and heat in Fujiwara). None of the references addresses the effect of inactivation procedure on the immune modulator activity of *P. acnes*. Therefore, the references provide no motivation to one skilled in the art to modify the inactivation procedure by terminal sterilization. Although

terminal sterilization is a well known method of inactivation, it is equally well known that the sterilization procedure may affect the pharmaceutical effectiveness of the sterilized material. The impact of sterilization on a particular material is generally unpredictable and needs to be experimentally tested. In addition, one of the major problems in applying experimental drug that is effective in animal studies to human treatment is safety concerns. In the present invention, applicants have demonstrated the safety of using terminally sterilized *P. acnes* at the therapeutic doses in humans (Example 4).

The Examiner indicated during the interview that the specification only provides working examples using *Propionibacterium acnes* but not other bacterial strains. Applicants respectfully submit that it is well-known for one skilled in the art that the claimed bacterial strains are closely related to each other and share similar immune-stimulation effect. Specifically, *Corynebacterium parvum* is the former name of *Propionibacterium acnes* (See Stedman's Medical Dictionary, 26 edition, 1995). *Arachnia propionica* is the synonym *of Propionibacteriu propionicus* (See Stedman's Medical Dictionary, 26 edition, 1995). According to A WEB-SURFER'S GUIDE TO BACTERIA ASSOCIATED WITH INFECTIONS IN HUMANS at http://freepages.pavilion.net/tetrix/welcome.html, *Propionibacterium acnes, Propionibacterium avidum, Propionibacterium lymphophilum, Propionibacterium granulosum,* and *Propionibacteriu propionicus* are all *Propionibacterium* species associated with same infections, such as acne vulgaris, and are all susceptible to glycopeptides, penicillin, and macrolides [see Funke, G., *et al.* (1997). Clinical microbiology of coryneform bacteria. Clin. microbiol. Rev. 10, 125-159. - Riley, T.V., Ott, A.K. (1981)]. Moreover, it has been reported that *Propionibacterium acnes, Propionibacterium avidum,* and *Propionibacterium granulosum* all stimulate lymphocytic and macrophagic functional activity (Roszkowski *et al.*, Zentralbl Bakteriol A. 246:393-404, 1980), and that all three species were effective in inhibiting the growth of Sarcoma 180 in CFW mice but were ineffective in inhibiting the growth of MSV tumor in adult NMRI mice (Roszkowski *et al.*, Zentralbl Bakteriol A. 246:405-414, 1980).

Taken together, Applicants respectfully submit that the therapeutic effect of *P. acnes* on skin diseases caused by the human papilloma virus and infections of the upper-and-lower respiratory tract is a novel property not disclosed by the prior art references, and that independent

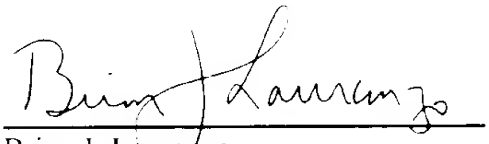
claim 1, as amended, is not obvious over the cited prior art references. Accordingly, withdraw of the 35 U.S.C. 103 rejections is respectfully requested.

CONCLUSION

In view of the above remarks, it is respectfully submitted that this application is in condition for allowance and such action is earnestly solicited.

Respectfully submitted,

Date: 9/9/03



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